REMARKS

Claims 35-52 and 63-64 have been examined. New claims 68-72 have been added. Claim 35 has been amended to limit the "fragment, mutant or variant" to the Tat Cys 22 mutant, as supported by the final paragraphs on page 12, and in the paragraph spanning pages 18 and 19 (e.g., last line of page 18). Page 19, line 18, specifically refers to this mutation as a "point mutation." Claim 35 also now requires that the "V3 loop is exposed or available and thereby bound to a binding region on the second peptide to form the complex." This reflects the nature of the exposure of the V3 loop which leads to the required binding (or to use the previous wording "coordination") of the *exposed* V3 loop with Tat, and it is supported at page 9, line 21 and page 4, line 11. Similar amendments have been made to the second claim, claim 36.

Claim 40 has been amended in a similar manner to claim 1. New claim 68 has been added, reciting a Tat Cys 22 mutant of residues 21-60 of Tat (SEQ ID NO 1), with support found in the paragraph following Table 3 on page 19 which refers to "transactivation domain, the core region and the basic region" of Tat which are defined on page 17 (lines 8-10) as being residue 21-60, and further support found in the paragraph spanning pages 5 and 6.

Claim 55 has been amended to exclude antibodies that bind to a complex lacking Tat. Given that the presence of Tat in a complex is the whole point of this application, support for this clarifying amendment is implicit in the application as filed.

New claims 69-73 have been added in an attempt to assuage the Examiner's objections in a different manner. Claim 68 is essentially the new main claim with the features of claims 42-45 inserted in Markush wording. Support for the trimeric Env is found on page 22 of the application. Claims 70-72 are supported by claim 35 and claims 46-47 and 52.

None of the amendments made herein constitutes the addition of new matter.

The Status of the Claims

Applicants have identified the status of claims 53-56 and 65-67 as withdrawn, in accordance with the request of the Examiner.

The Invention

Applicants respectfully reiterate the following discussion of the claimed invention to facilitate the discussion of the rejections and to make clear the basis of the invention as claimed.

The present invention relates to the discovery that Tat binds to Env/gp120, **only** occur when the V3 loop is exposed. From this discovery flows the use of a Tat-gp120 complex for use an immunogen and in immunogenic compositions and methods. Consistent with the novelty of the present invention, the last paragraph of page 22 of the Specification discusses new B cell epitopic determinants for the Tat/Env complex, formed via the V3 loop.

The Rejections under 35 U.S.C. 112, first paragraph

Claims 35, 37-50, 52, 63 and 64 remain rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the requirement for written description. Applicants respectfully traverse this rejection.

The Patent Office has said that the rejection was made because the claims are interpreted as being drawn to a genus of peptides recited as fragment, mutants or variants thereof. The Patent Office has concluded that there is insufficient recitation of distinguishing identifying characteristics.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claims 35 and 40 to specify a particular mutation site in the Tat protein. This same limitation occurs in new claims 69 and 70.

It is believed that this amendment should overcome the rejection, and Applicants respectfully maintain that one of ordinary skill in the art, reading the claims and the instant Specification, understands that the inventors were in full

possession of the invention as claimed. In view of the foregoing discussion and the amendments to the claims, Applicants respectfully maintain that the requirements of the statute are met, it is clear to the skilled artisan that the inventors were in possession of the invention as claimed at the time the application was filed, and the rejection should be withdrawn.

The Rejections under 35 U.S.C. 112, second paragraph

Claims 35, 37-52, 63 and 64 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Patent Office has alleged that the recitation of fragment, mutant or variant thereof renders the claims indefinite because "one would not know what type of fragment, mutant or variant thereof would be immunogenic or capable of binding the specified residues of SEQ ID NO:1 or 2."

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claims 35 and 40 to specify a particular site of mutation in the Tat protein (i.e., the Cys at position 22 of SEQ ID NO:1). It is believed that this is resolves the rejection. Note that this same limitation is part of new claims 69 and 70.

In view of discussion in the present response and with the amendments to claims to better claim the invention, Applicants respectfully maintain on the record that the claims are sufficiently clear and definite as to fulfill the statutory requirements, particularly in the eyes of the skilled artisan reader of the present application. Accordingly, the rejection under 35 U.S.C. 112, second paragraph, should be withdrawn.

The Rejections under 35 U.S.C. 102

Claims 35-40, 42, 45, 50-51, 63 and 64 have been rejected under 35 U.S.C. 102(b) as allegedly unpatentable over Voss et al. (WO 01/54719). Applicants

respectfully traverse this rejection.

Traverse is made below the listing of all the Section 102 rejections.

Claims 35-40, 42, 45, 50-51, and 63 have been rejected under 35 U.S.C. 102(b) as allegedly unpatentable over Voss et al. (2003) J. Virology 77:1049-1058. Applicants respectfully traverse this rejection.

Claims 35-42, 45, 50-52, 63 and 64 have been rejected under 35 U.S.C. 102(b) as allegedly unpatentable over Debrus et al. (WO 02/087614). Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claims 35 and 40 to recite "the first peptide **comprising** the V3 loop of gp120, and wherein the V3 loop is bound exposed or available and thereby bound to a binding region on the second peptide to form the complex". New claims 69 and 70 recite this language, as well. This conveys the availability of the V3 loop for binding. The importance of this property of the V3 loop within the complex is discussed below.

None of the cited references teaches the necessity for the accessibility of the V3 loop, nor do any of the cited references teach conditions which would make the V3 loop available for binding to the Tat protein. There cannot be any complex formation between Tat and Env in the cited references because none of the conditions required for V3 loop exposure or availability (required by binding Tat) are present in either of the Voss citations. Furthermore, none of the cited art recognizes that Tat mimics the CCR5 co-receptor.

The first cited Voss reference (WO) does not disclose complexes of Tat bound to the V3 loop of Env, and the conditions taught by Voss are not conducive to the formation of such complexes. In Voss, the Tat cysteines are modified to prevent the formation of disulfide bonds. This modification, in itself, prevents any interaction with the V3 loop even if the loop were exposed. Thus, this Voss reference actually

teaches away from the present claimed invention. The cited Voss reference makes no teaching of the particular compositions (or methods of use) or even of their desirability. Neither does Voss appear to teach any conditions which would result in the accessibility of the V3 loop. Accordingly, the cited Voss reference cannot be properly deemed to anticipate the present claimed invention and the rejection must be withdrawn.

Applicants respectfully note that SEQ ID NO:1 is the Tat sequence, while SEQ ID NO:2 is the gp120 sequence. Thus, the main claim can be paraphrased to equate to the gp120 loop bound to the appropriately specified region of Tat. While the Specification makes several references to the Env protein, it is more accurate to refer to the gp120. Because the claims specify that the V3 loop of the first peptide is bound to the binding region of the second peptide, which can be Tat or mutants, variants or analogs thereof, the claims are not anticipated by the cited Voss reference. It is understood in the art that it is not possible for a complex between Tat and Env (gp120) to form unless a V3 loop is exposed, and this does not occur with simple mixtures of Tat and Env/gp120, as in Voss. Applicants emphasize that Voss only teaches such simple mixtures. The present Specification teaches that the V3 loop can be made available by mutation (for example in the ΔV2 mutant) or by interacting Env/gp120 with CD4, for example. None of the cited references teaches the necessity for the accessibility of the V3 loop nor do any of the cited references teach conditions which would make the V3 loop available for binding to the Tat protein. In fact, none of the cited art recognizes that Tat mimics the CCR5 co-receptor.

As to the cited Debrus reference, Debrus requires an HIV antigen in conjunction with an HSV or HPV antigen. This is not the same invention as claimed. Debrus teaches no condition under which the V3 loop would be made accessible for binding. Thus, Debrus does not teach conditions under which the Tat-Env complex of the present invention could form. In sum, the cited Voss reference makes no teaching of the particular compositions (or methods of use) or even of their desirability. Neither does Voss appear to teach any conditions which would result in the accessibility of the V3 loop. Accordingly, the cited Debrus reference cannot be

properly deemed to anticipate the present claimed invention and the rejection must be withdrawn.

The second cited Voss reference discloses different mixtures of antigens (Table 1), but there is no disclosure of any condition or treatment that would make the V3 loop of gp120 accessible for binding to any portion of the Tat protein. As above, there is no anticipation of the present claims which require the accessibility of the V3 loop for binding to the Tat protein. Thus, no complex could form and not every feature recited in the instant claims is present in the reference, and thus, the rejection is not proper and should be withdrawn.

In view of the foregoing, none of the cited references anticipate the claimed invention, and the three rejections for alleged anticipation must be withdrawn.

The Rejections under 35 U.S.C. 103

Claims 41, 42-44, 46-49 and 52 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Voss et al. (WO 01/54719) or Voss et al. (2003) J. Virology 77:1049-1058 as applied to claim 35 above and further in view of Gzyl et al. (2004) Virology 318:493-506, Wyatt et al. (1995) J. Virology 69:5723-5733, Sattenau et al. (1993) J. Virology 67:7383-7393, Ibrahim et al. (1999) Virus Research 60:159-169 and Watanabe et al. (2000) Vaccine 19:1199-1203. Applicants respectfully traverse this rejection.

Applicants respectfully refer the Examiner to the Specification at page 2, where it is stated:

> Surprisingly, we have found that Tat can interact with the gp120 V3 loop, thereby mimicking the CCR5 co-receptor, both at the molecular (structural) and functional level, thereby conferring on CCR5-tropic HIV strains the ability to infect cell targets expressing only very low amounts of CCR5, and which would not be infected with the same virus input, in the absence of immobilised Tat.

As noted above, there is no teaching of the necessity of making the V3 loop accessible, nor is there any teaching or suggestion of conditions that would make the V3 loop accessible for binding to Tat in either of the cited Voss references. Until the

finding that Tat could interact with the V3 loop of Env, mimicking the CCR5 receptor, both at the molecular (structural) and functional levels, no one in the art would have seen any benefit or purpose to using an exposed V3 loop bound to Tat in any immunogenic compositions.

With respect to the cited Gyzl and Wyatt references, while these may disclose the advantage of various mutants of the Env/gp120 protein and the role of the V2 loop, there is still nothing in these references to suggest that Tat mimics the CCR5 receptor or that Tat binds gp120 via the V3 loop. Gyzl and Wyatt focus on ways to improve the immunogenicity of Env and its cleavage product gp120. The cited Voss references do not teach conditions which would expose the V3 loop or otherwise allow the binding of Tat and gp120 or peptides thereof, and the Gyzl and Wyatt references are focused on Env and do not teach or suggest that the V3 loop of gp120 can bind Tat (or any advantage of such binding). Sattenau teaches that CD4 can induce the exposure of the V3 loop of gp120, but it is silent as to the binding of the exposed V3 loop to Tat. Ibrahim discusses heparin sulfate and Watanabe discusses cross-liking peptides, but neither appears to be germane to the base claims. In the absence of a motivation to expose the V3 loop as relates to binding to Tat, one of ordinary skill in the art would not have been motivated to combine these teachings to arrive at the present invention. There is no indication as to why one would have done so.

Applicants acknowledge that there is a substantial body of prior art related to HIV and potential vaccines. However, no one is believed to have identified the role of Tat as presented in the present application, with its mimicry of the CCR5 receptor and the importance of Tat/Env binding via an exposed V3 loop. Thus, there was no motivation to make the complexes or input components of the complexes, and therefore, the present invention as claimed is not obvious over the cited references.

In view of the foregoing, Applicants respectfully maintain that the present invention is not prima facie obvious over the cited references and request the withdrawal of the rejection.

Claims 43-44 and 46-49 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Debrus et al. (WO 02/087614) as applied to claim 35 above and further in view of Gzyl et al. (2004) Virology 318:493-506, Wyatt et al. (1995) J. Virology 69:5723-5733, Sattenau et al. (1993) J. Virology 67:7383-7393 and Ibrahim et al. (1999) Virus Research 60:159-169. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claims 35 and 40 to recite "the first peptide **comprising** the V3 loop of gp120, and wherein the V3 loop is bound exposed or available and thereby bound to a binding region on the second peptide to form the complex". New claims 69 and 70 also recite this language.

Note that the Specification (page 2, third full paragraph, and page 4, first full paragraph) states that it was a surprising result that Tat interacts with the gp120 V3 loop, where the V3 loop is available to bind a region of the second peptide in the complex as claimed.

As a first matter, and previously discussed, the Debrus reference does not teach or suggest conditions which would make the V3 loop of gp120 accessible for binding to Tat. In the absence of that accessibility, there can be no such binding. None of the cited references teach the binding of Tat with the V3 loop or the desirability of a complex or a V3-exposed gp120 protein or peptide. The references other than Debrus have been discussed above, and Debrus certainly does not add what those references lack, any more than do the Voss references (or vice versa).

In view of the foregoing arguments and the teachings of the Specification, for example, at page 2, where the inventors state that the binding of the V3 loop of gp120 was unexpected and the long felt need in the art for vaccines against the AIDS virus, Applicants respectfully submit that the present invention as claimed is not obvious over the cited references.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Request for Continued Examination, a Petition for Extension of Time (three months) and payment in the amount of $1,110.00 as required under 37 C.F.R. 1.17(a) and $810 as required by37 C.F.R. 1.17(e). It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount submitted is incorrect, however, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,

/donnamferber/

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